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Challenges and recent progress in tropical disease drug discovery

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Preface

Infectious tropical diseases cause a huge toll in terms of mortality and morbidity, as well as a large economic burden to the countries concerned. These diseases predominantly affect the world's poorest people. Unfortunately, current drugs are inadequate for the majority of these diseases, and there is an urgent need for new treatments. In this review, we discuss some of the challenges involved in developing new drugs to treat these diseases and highlight recent progress. Whilst there have been notable successes, there is still a long way to go.

1. Introduction

Infectious tropical diseases mainly affect Low and Middle Income Countries (LMICs). The symptoms range from impaired cognitive and physical development in children (Box 1), complications in pregnancy, fever, nausea, diarrhea, dehydration, anemia, rashes, lesions, deformities, blindness, organ failure, haemorrhaging, neurological problems, seizures and coma and in many cases death. In 2015 the WHO estimated that the diseases listed in Figure 1, were responsible for over 4 million deaths[1] and over 250 million years lost due to ill-health, premature disability or early death (DALYs – disability-adjusted life years)[2].

Infectious tropical diseases include those defined by the World Health Organisation (WHO) as neglected tropical diseases (NTDs), listed by an asterisk in text below[3]. In addition, diseases such as malaria, tuberculosis (TB), HIV/AIDS, multi-drug resistant Gram-negative bacterial infections, diarrhea (from a variety of pathogens), and hepatitis also disproportionately affect tropical countries. Whilst not an exhaustive list, the most common tropical diseases are: (i) ***viruses****:* chikungunya*, dengue*, ebola, HIV-AIDS, Lassa fever, Marburg, rabies*, Rift Valley, yellow fever, Zika disease. (ii) ***bacteria****:* bubonic plague, Buruli ulcer*, leprosy*, mycetoma*, shigellosis, trachoma*, TB, typhoid, typhus, yaws*, drug resistant Gram-negative bacteria. (iii) ***protozoa****:* Chagas' disease*, cryptosporidiosis, human African trypanosomiasis*, leishmaniases* (visceral, cutaneous, post kala-azar dermal and mucocutaneous), malaria. (iv) ***fungi***: cryptococcosis, mycetoma*. (v) ***helminths or metazoan worms****:* cysticercosis/taeniasis*, dracunculiasis*, echinococcosis*, foodborne trematodiases (clonorchiasis, opisthorchiasis, fasciolosis)*, lymphatic filariasis*, onchocerciasis*, schistosomiasis*, soil-transmitted helminthiasis* (ascariasis, hookworm, trichuriasis, strongyloidiasis), guinea worm*. Co-infection is commonplace, and this can exacerbate symptoms and complicate treatments (Box

2).

Infectious tropical diseases inflict a high economic burden, costing LMIC economies billions of dollars every year. By way of example, it was estimated in 2013 that the annual global cost of dengue was US$8.9 billion[4], whilst a study in the Philippines indicated each case schistosomiasis resulted in an average loss of 45.4 days of work per year[5].

For many of these diseases the current treatments are unsatisfactory ande there are few or no suitable drugs. Without doubt, there is an urgent need for new, safe, low cost, efficacious medicines. Tackling these diseases effectively requires an integrated multi-sectoral approach, linking chemotherapy with prevention initiatives such as improved water supply, sanitation and hygiene, vaccines and vector control. Various governmental and non-governmental organisations, charities, foundations, product development partnerships, academic groups and pharmaceutical companies support tropical disease drug discovery. A breakdown of funding is summarised in the G-Finder[6] and IFPMA 2017[7] reports. In 2014 about two-thirds of the total funding for research and development for neglected diseases as recorded by G-Finder ($3,377 million) was spent on HIV/AIDS (34%), malaria (18%) and TB (18%). Overall R&D funding has significantly increased in the last decade but gains are not shared equitably across diseases. Given the huge unmet medical need, greater effort, resources and funding are still required.

In this review, we will consider the specific challenges associated with tropical disease drug discovery and examine some of the recent successes.

2. Discovery Pathways and Challenges

The drug discovery pathway

The pathway for a typical small molecule drug discovery programme for an infectious disease is shown in Figure 2. The first step is to identify chemical start points (*Hit Discovery*). This usually involves screening collections of compounds against a molecular target, typically an enzyme (target-based screening) or against whole organisms (cell-based or phenotypic screening). Other hit discovery approaches include structure-based drug discovery, re-purposing of drugs from other disease areas, or *in silico* methods. *Hit Expansion* is carried out to verify that the hit is genuine and that there is scope for further work with the chemotype. The compound is then refined through a cyclic process of 'design – make – test' (*Hits to Lead*), until it

has significant activity in an animal model of infection. After this, the *Lead Optimisation* phase optimises and balances the biological activity, the pharmacokinetics and the safety profile of the series. *Candidate Selection* marks a significant milestone in the early stage drug discovery pathway as it involves selecting one compound for progression. Regulatory toxicology and scale up are carried out to enable first in human studies. In human *Clinical Trials*, the compound is tested first in healthy volunteers to measure pharmacokinetics and safety (Phase I), followed by studies to establish efficacy (Phase II), and then large-scale efficacy and safety studies (Phase III).

Target Product Profiles and Compound Progression Criteria

Target Product Profiles (TPP) should guide the drug discovery pathway. They describe the desired features required of the final drug product, such as duration of treatment, whether the treatment is oral or parenteral, cost of treatment, acceptable safety margins, etc[8]. TPPs have been defined for malaria[9], leishmaniasis[10], human African trypanosomiasis[10], Chagas' disease[11], cryptosporidiosis[12] and dengue[13], but are absent for many other diseases, hampering the drug discovery process. The TPP is used to develop *Compound Progression Criteria,* which informs the required disease-specific profile of a compound at every step along the drug discovery process. These include for example, activities in particular assays, pharmacokinetic profiles, and selectivity parameters[8]. Medicines for Malaria Venture (MMV) has excellent examples of Compound Progression Criteria on their website.

Challenges

For many tropical infectious diseases, there is little or no precedent in developing small-molecule drugs, which is exacerbated by insufficient understanding of the pathogen biology. As a result, there are often no relevant cellular models or predictive animal models of the human disease. There is often little or no data from clinically active molecules to help understand what profile a new drug should have with respect to activity in preclinical assays, animal models and its pharmacokinetic profile. The key issues facing researchers seeking to discover new drugs to treat tropical diseases, are summarised in Figure 2, and will be considered below.

Biology Challenges

There are very few well-validated molecular drug targets for tropical diseases, in

part due to a lack of understanding of the detailed biology of many of the pathogens. For example, the function of many proteins is unknown, or is only inferred from other organisms. Therefore a key challenge is selecting a suitable molecular target, to limit the risk of later failure[8]. Criteria to assist with selecting appropriate targets include essentiality, druggability, assayability and the opportunity for selectivity over host orthologues[8]. Even if a target complies with all these criteria, inhibitors frequently fail to demonstrate cell-based activity due to poor permeability, inability to compete with high substrate concentrations in cells or because the compounds cannot inhibit the target sufficiently to kill the pathogen. The deficiency of genetic tools for many disease-relevant organisms is a key reason why so little essentiality data is available. However, new technologies are emerging[14-16], including CRISPR/Cas9[17,18], which offer the prospect of significantly increasing the number of validated targets available in the near future.

Large-scale cell-based (phenotypic) screening is currently a popular screening approach to identify new chemical start points, as it does not require prior knowledge of the molecular target[19,20]. Developing assays that have sufficient throughput to allow compound library screening that maintain relevance to disease pathophysiology is challenging, but helps to reduce attrition in *in vivo* models and ultimately the clinic[21]. As assays improve in relevance they usually become more complex requiring substantial resources both in terms of specialist equipment and staff to develop and run the assays. Other challenges can be the lack of robust *in vitro* culture systems (for example *Cryptosporidium*); the inherent safety challenges of handling disease-causing agents in bulk; the lack of standardisation between different laboratories working on the same organisms; and the use of lab-strains and cell lines rather than recent clinical isolates and primary cells[21,22].

Existing animal models of these infections are often poorly representative of the human disease. For example in onchocerciasis (river blindness), the worm (*Onchocerca volvulus)* is only infective to primates; consequently related, but different, worm species are used in mice or cattle models. Human malaria does not infect rodents normally; however a SCID mouse model has been developed that can be infected by human falciparum malaria[23]. Work is also ongoing to develop a mouse model of human vivax malaria[24]. Most normal mouse models of TB do not replicate the human disease well, and the mice do not form the granulomas which are typical of human disease. Encouragingly progress is being made on developing animal models that more closely replicate human pathology[25-27].

Recent human clinical trials in Chagas' disease with azoles, which inhibit the

enzyme CYP51, have not been successful. A mouse model has now been developed that can distinguish between benznidazole, known to have clinical efficacy and an azole (posaconazole) that does not[28]. Better differentiation at this preclinical stage should improve clinical trials success rates.

Quiescence and Dormancy

Dormant infections further complicate some diseases. In malaria, *P. vivax* and *P. ovale* can remain dormant (hypnozoites) in hepatocytes of the human host for weeks to years, causing relapse[29]. Latent tuberculosis with absence of clinical symptoms but a risk of progression to clinical disease is estimated to affect one third of the global population[30]. Recently dormancy has been identified in *Trypanosoma cruzi*[31]. Quiescent and dormant pathogens have reduced metabolism compared to actively dividing pathogens and can be less susceptible to drugs. Developing assays for these forms of the pathogens is problematic. To effectively treat and eliminate these diseases, the challenge is to develop new drugs that effectively tackle the reservoir of dormant and quiescent infections.

Chemistry Challenges

It is essential that the compound can be dosed appropriately, usually orally, and reach the region of the body where the pathogen is located. The physicochemical properties of a molecule, such as molecular weight, solubility, lipophilicity, charge, number of hydrogen bond donors and acceptors are key in achieving this.

In some cases, the penetration of the compounds into the pathogen is problematic. For example, Gram-negative bacteria are surrounded by an outer-membrane; compounds can penetrate this through porins, which tend to let in hydrophilic molecules. Molecules then have to traverse the cell membrane, a lipid bilayer, which requires compounds with a degree of lipophilicity. Therefore to penetrate into the cytoplasm, compounds probably need to have very defined chemical properties, likely to be more polar and charged than typical drugs[32,33]. Having penetrated to the cytoplasm, there is then a risk of being pumped out of the bacteria through efflux transporters. Other pathogens such as *Trypanosoma cruzi, Chlamydia trachomatis, Mycobacterium tuberculosis* and viruses spend the majority of their life-cycle inside human host cells, which may hamper drug access. Some even localise to extreme environments such as acidic intracellular organelles (*Leishmania spp., Salmonella spp.*) and necrotic granulomas (*M. tuberculosis*). In the latter case a significant challenge is drug penetration through non-vascularised lipid-rich caseum

to access the pathogen[34]. Other infections are localised at sites protected by a blood-tissue barrier, such as the central nervous system (HAT, *Cryptococcus neoformans*, encephalitis/meningitis causing viruses/bacteria, *Taenia solium*) and eyes (*Chlamydia trachomatis*). To reach these sites drugs need to pass through endothelial cells without being immediately pumped back into the blood by P-glycoprotein[35].

By nature of these diseases, the cost of treatment must be low. For malaria, the aim is to produce a treatment that costs less than US$1. To achieve this, a short and cheap chemical synthesis is required and complex formulations to counter issues such as poor solubility are precluded. Due to the lack of cold-chains in many regions, compounds are required that are stable over long periods of time at high temperatures (>40°C) and high humidity. Finally, patient compliance is challenging, compounded by often minimal medical support. As a result, minimising the number of doses and complexity of dosing regimens is essential. For example, MMV is aiming for a single dose treatment for bloodstream malaria[9].

Resistance

Drug resistance is a significant problem for most infectious diseases, in particular for viral, bacterial and apicomplexan infections[36-38]. Poor usage of treatments can accelerate the occurrence of resistance. The most notable example at the moment is antibacterial drug resistance. In humans, antibiotics are sometimes taken when not required, or given at sub-therapeutic doses, potentially increasing the proportion of resistant bacteria within a pathogen population. This problem is aggravated by the large amounts of antibiotics in the environment due to indiscriminate use in agriculture and aquaculture.

In an attempt to slow down resistance, combination therapy is being adopted in many diseases. This has been particularly successful in HIV/AIDS where the resistance rate for single therapy[39] is incredibly high. Combination treatment has also proved very effective in TB and malaria. Worryingly, in the case of malaria, resistance is now arising in Southeast Asia to artemisinin combination therapy, the mainstay for treatment[38]. There is a need for drugs with novel modes of action to deliver new combination therapies with no clinical resistance to any of the components of the therapy.

3. Progress

Despite all these challenges, progress is gradually being made. Some examples are highlighted below, although our coverage is not complete. The successes are due

to coordinated and substantial investment into research, along with concerted efforts to understand the TPPs and drug discovery pathways.

Apicomplexans

With 200 million cases of malaria a year, the human and economic cost of malaria is extremely high[40]. Africa carries a disproportionately high share of the burden with over 400,000 deaths a year. Multiple new types of antimalarial are needed to: overcome resistance; give single dose treatments; prevent relapse of *P. vivax* infections; block transmission; and act as chemopreventatives. The malaria drug discovery portfolio has dramatically improved over the past decade[41]. The starting points for the majority of the compounds currently in development were identified by phenotypic screening in collaborations with MMV. In many cases target-deconvolution has subsequently led to the identification of the molecular targets. There are a number of novel compounds in clinical trials supported by or in collaboration with MMV (Figure 3). The following are derived from phenotypic screens and in Phase II trials: the spiroindolone KAE609, the imidazolopiperazine KAF156[42] (combination trial with lumefantrine), the synthetic trioxolane artefenomel (OZ439) in combinationwith ferroquine[43] and the 2-aminopyridine MMV048. The mode of action has been determined for some of these (*Pf*ATP4 for KAE609[44], *Pf*PI(4)K for MMV048)[45], while the mode of action of KAF156 and OZ439 remains uncertain; KAF156 has been linked to cyclic amine resistance locus (*Pfcarl*)[46] and OZ439 probably acts through formation of carbon radicals, whilst ferroquine acts to prevent heme detoxification. In Phase I trials are: the dihydroisoquinoline SJ733, which is another *Pf*ATP4 inhibitor[47]; and M5717 which is active against translation elongation factor 2[48]. Two compounds derived from target-based projects are also in clinical trials: the dihydroorotate dehydrogenase inhibitor DSM265[49], which is in Phase II trials, and P218, a dihydrofolate reductase inhibitor, which is in Phase I trials.

We envisage an increase in target-based drug discovery as mode-of-action studies are revealing the chemically validated targets of many of the recently identified phenotypic hits. A consortium led by Winzeler is systematically trying to find the mode of action of phenotypic hits[50]. Recently, new types of phenotypic screens have been developed which target life-cycle stages in addition to or other than the asexual blood stages[51,52]. Clinical development for malaria has accelerated thanks to the development of human challenge models in which healthy volunteers are infected with treatable malaria to obtain an early indication of drug efficacy[53,54].

Cryptosporidiosis has been shown to be a major cause of diarrhea in children in

tropical countries (Box 1). Nitazoxanide, the current treatment for the disease, has variable efficacy in immunocompetent patients and is not effective in immunocompromised patients[55,56]. There is an urgent need for the development of new drugs to treat children under 24 months, especially those that are malnourished and suffering from chronic diarrhea.

There have been recent advances in the cryptosporidiosis discovery pipeline. A series of bumped kinase inhibitors of *Cryptosporidium parvum* calcium-dependent kinase 1[57], an example of which is BKI1534, has been developed. Promisingly, recent advances in *C. parvum* high-content imaging infection assays in human intestinal epithelial cells have made phenotypic screening of medium and large size compound libraries possible. A screen of compounds active against malaria has led to the identification of a preclinical candidate KDU731[58], an inhibitor of *Cryptosporidium* phosphatidylinsoitiol 4-kinase. Clofazimine, an approved drug for the treatment of leprosy, was identified from a screen of bioactive compounds[59] and is entering clinical trials for cryptosporidiosis.

Kinetoplastid diseases

We have recently reviewed this area in detail[60]. Mortality rates for human African trypanosomiasis (HAT/Sleeping Sickness) have decreased substantially in recent years[61], but there is still a significant disease burden in central Africa. The advent of NECT (nifurtimox-eflornithine) combination therapy in 2009 marked an important step in the treatment for stage 2 *T. b. gambiense* HAT. It reduced the duration of treatment as well as decreasing adverse effects[62]. Nevertheless, treatment is still problematic because the two forms of the disease (*T. brucei gambiense* / *T. b. rhodesiense*) and the two stages (acute / CNS) require different drugs[61]. The requirement for staging patients prior to treatment also limits uptake, as it involves a painful and technically challenging lumbar puncture[63]. The on-going development of two new drugs has the potential of transforming the clinical management of HAT[64]. The first is fexinidazole, a nitroaromatic compound developed in the 1970s and 1980s as a broad-spectrum antibiotic, was more recently found to have a suitable profile for clinical development for HAT[65]. Drugs for Neglected Diseases initiative (DNDi) completed a Phase III clinical trial in 2017 and reported non-inferiority over NECT for both stages of the disease with a 10-day oral treatment[66]. The second is an oxaborole compound, SCYX-7158 (acoziborole)[67], currently undergoing a pivotal Phase II/III trial[10]. This has potential to give a single dose oral

treatment for all forms of HAT.

For leishmaniasis and Chagas' disease, less progress has been made. In the Indian subcontinent, current treatments, particularly liposomal amphotericin-B, together with other measures such as vector control and effective surveillance, may offer the possibility of elimination of visceral leishmaniasis (VL)[68]. However, the current drugs are less effective or unsuitable in other areas of the world. New oral drugs are urgently needed to treat VL in these regions and to provide improved treatment options in the Indian sub-continent. HIV-VL coinfection is also poorly treated. Several oral treatments identified through phenotypic screening are in preclinical development. These include an oxaborole and a nitroimidazole[69]. Notably the discovery of a pan-kinetoplastid proteasome inhibitor (GNF6702, Fig. 3)[70] offers potential for development of new drugs for leishmaniasis, Chagas' disease and HAT. The majority of leishmaniasis preclinical work focuses on VL, the deadly form of the disease, rather than cutaneous leishmaniasis (CL). New oral therapies are urgently needed for CL as well. Chagas' disease research suffered a recent setback resulting from the clinical failures for the CYP51 inhibitors posaconazole and fosravuconazole[71,72]. Currently, the pipeline for this challenging disease is sparse.

Viruses

Viruses such as HIV, hepatitis C (HCV), dengue and rabies have significant global impact (Figure 1) resulting in over 1 million deaths in 2015 (WHO 2015). Effective treatments for HIV and HCV have been developed[73,74]. Other viruses, including flaviviruses, arenaviruses, coronaviruses and filoviruses still pose a significant threat for tropical countries and beyond with a particular risk for global pandemics; as exemplified by the recent outbreaks of Zika[75], chikungunya[76], dengue[77], ebola[78] and MERS[79]. Since future epidemics are almost inevitable, and could be triggered by any member of these families, drug discovery efforts rightly focus on broad-acting antivirals[80]. In terms of small-molecule drug discovery, these diseases have received relatively little attention. However, both target and cell-based hit discovery approaches have yielded new compounds of interest, but to date none of these have progressed anywhere as far as the HCV and HIV drugs[80]. The most advanced compounds are favipiravir, GS-5734 (remdesivir) and BCX4430 (galidesivir) that target the viral polymerase (Fig. 3). Favipiravir was tested in humans during the ebola virus epidemic of 2014, and while conditions complicated the study, it was concluded that further investigation was warranted[81]. GS-5734 has shown activity in a rhesus monkey model of Ebola[82], and was also used in humans during the 2014 Ebola

outbreak. It is currently undergoing a phase II clinical trial in West Africa. Both favipiravir and GS-5734 are being considered for use in the 2018 Ebola virus outbreak in the Democartic Republic of the Congo[83]. BCX4430 has demonstrated complete protection against Marburg virus in non-human primates and against Ebola in rodent models, when administered within 48h of infection. This compound also shows broad activity against other viruses including arenaviruses and flaviviruses[84,85] and is currently in clinical development. Inhibitors targeting the viral protease are not as far advanced (with the exception of HIV and HCV). They also show promise as broad-spectrum antivirals. The potential of targeting host pathways is also being explored[80,86]. While new small-molecule antivirals are being discovered, there clearly is an urgent need to translate more of them into the clinic, alongside on-going vaccine development.

Bacterial diseases

Tuberculosis continues to be a major problem across the world. As with malaria, treatments for TB are given as combinations to combat resistance, and can circumvent issues with TB residing in multiple environments and metabolic states. The need for combination therapy complicates the progression of new compounds through clinical trials[87]. Recently two new drugs, bedaquiline and delaminid, have conditionally approved for the treatment of specific levels of drug-resistant TB on the basis of phase IIb trials and are currently undergoing phase III studies[88]. Bedaquiline targets the ATP synthase[89] and is active against the latent forms of the bacterium[90]. Delamanid is a nitro-heterocycle. Its precise mode of action has not been determined, but it is probably a prodrug that needs activation within the bacterium. It has been implicated in inhibition of mycolic acid biosynthesis; which is critical for the structure of *M. tuberculosis* cell wall[91,92].

A number of other compounds are currently under development for TB[87,93] that target protein synthesis, the respiratory chain and the cell envelope. Several different steps in protein synthesis are being studied. Recently, linezolid has been shown to be active against drug-resistant TB, and has significant effect on patients with extensively drug-resistant TB[94]. This is one of the oxazolidinone class of molecules which targets the 50S ribosomal subunit. However, adverse effects are associated with the extended treatment periods with linezolid that are required for multi-drug-resistant TB. This is linked to mitochondrial toxicity[95]. Other oxazolidinones, such as sutezolid and delpazolid are undergoing clinical trials[88]. Avoiding mitochondrial toxicity should allow development of compounds with better tolerability. A

collaboration between Anacor and GSK, has given rise to a series of oxaboroles[96]. One of these compounds GSK070, which inhibits leucyl-tRNA synthetase, an enzyme involved in protein synthesis, is being progressed in clinical trials. The compound forms a covalent adduct with the 3'-adenosyl acceptor nucleotide of the tRNA, with the boron binding to the 2'- and 3'-hydroxyl groups. This complex is formed in the editing site, inactivating the enzyme.

Q203 has just entered clinical trials and targets the respiratory pathway, inhibiting cytochrome bc_1 (QcrB)[89]. This is on the same pathway targeted by bedaquiline, although at a different step. Hitting this pathway at multiple points appears to enhance killing of the bacterium[89].

In terms of cell wall biosynthesis, β-lactams are also being re-investigated for TB. Carbapenems appear to be the more attractive compounds, both from the proteins that they target and also as they are much weaker substrates of the *M. tuberculosis* β-lactamases. Several enzymes involved in cell envelope biosynthesis are promiscuous targets; DprE1 and MmpL3. The former is involved in the biosynthesis of an arabinogalactan polysaccharide which is critical for cell wall biosynthesis. Benzothiazones have been discovered to be covalent inhibitors of this enzyme; one of these compounds, BTZ043, is in preclinical development and another, PBTZ169 is undergoing clinical evaluation[93]. Two non-covalent inhibitors of DprE1 are also undergoing clinical evaluation, both in phase I, an azaindole TBA-7371 and OPC-167832. MmpL3 is required for the export of mycolic acid precursors, which are essential for cell wall biosynthesis. Compound SQ109 which targets this enzyme, and probably others[88], is in clinical trials[97]. InhA, which is an enoyl reductase and part of the fatty acid biosynthesis pathway, is involved in the biosynthesis of mycolic acid. Isoniazid is a prodrug, which when activated inhibits InhA, validating InhA as a drug target. Several preclinical drug discovery programmes are on-going to find direct inhibitors of InhA.

Pretomanid (PA-824) is a nitroimidazole which is in clinical trials. This compound is active against both replicating and non-replicating mycobacteria. This is probably a prodrug like delamanid. A number of other compounds[98] are undergoing clinical evaluation[93], and several fluoroquinolines are being investigated as part of combinations, including moxifloxacin and levofloxacin.

Whilst antibacterial drug resistance is not technically a neglected or tropical disease, the impact is most clearly seen in LMICs, which have very high levels of drug resistance. The WHO has recently published a priority list of pathogens[99]. The priority 1 pathogens are: *Enterobacteriaceae* which are resistant to carbapenems and 3rd

generation cephalosporins and *Acinetobacter baumannii* and *Pseudomonas aeruginosa* that are carbapenem-resistant. New drugs are urgently needed to tackle these diseases, but there is very little in clinical development that addresses the most urgently needed cases[100]. In addition to this there are bacterial infections such as shigellosis and typhoid, which are almost entirely found in LMICs. Drug resistance is a major issue here and worryingly in some cases, the resistant bacteria have a higher fitness than wild type bacteria[101,102]. Treatment is reliant on existing antibacterials.

Helminths

At least one billion people, and probably more, are estimated to have one or more helminth infection[103]. Yet the only new antihelminthic drug to emerge in the last 30 years is tribendimidine, which shows promising broad-spectrum activity. Recent clinical trials demonstrated that it is a suitable alternative for the benzimidazoles and praziquantel in various helminth infections[104-106]. Beyond this, development of new treatments is focused on repurposing drugs. This has mostly involved anthelminthics approved for veterinary use. Oxantel pamoate, a veterinary licensed drug since 1974, has recently shown promising efficacy results in clinical trials for trichuriasis (whipworm), one of the more difficult to treat soil-transmitted helminths[107], and in combination with albendazole and pyrantel pamoate, it has recently demonstrated high clinical efficacy against hookworm infections[108]. Two other veterinary drugs, emodepside and moxidectin, have promising activity against several human helminths and are currently undergoing clinical trials for onchocerciasis[69,109]. Some antimalarial compounds show activity against schistosomes *in vitro* and *in vivo*. Mefloquine-praziquantel and mefloquine-artesunate-praziquantial combinations were tested in clinical trials against chronic *S. haematobium* infection. Unfortunately, adverse event rates were high while there was no increased efficacy compared to praziquantel[110]. In the case of filarial worms, an alternative strategy is targeting the *Wolbachia* endosymbiotic bacteria, which results in slow killing of the worms hereby preventing serious adverse events. Four weeks of treatment with doxycycline cures people suffering from onchocerciasis. The major aim of Wolbachia-directed therapy is to find shorter course antibiotics[111]. To discover new chemical entities for helminth infections several high-throughput phenotypic screens have been carried out[112,113] but currently no new clinical candidates have been reported.

Fungal Infections

Fungal infections are particularly serious in immunocompromised patients. In addition to the common fungal infections, there are some fungal infections which are mainly found in tropical regions. One of the most significant problems is meningitis due to *Cryptococcus neoformans*, estimated to cause 180,000 deaths per year amongst HIV-infected people, the majority of whom are in Africa[114]. This is poorly treated and there is a need for new more efficacious drugs. Mycetoma, a disfiguring infection of the skin and soft tissue, is a particularly neglected disease endemic to tropical and subtropical areas. Mycetoma can be caused by bacteria (actinomycetoma) or by fungi (eumycetoma). Fungal mycetoma requires long treatment with azoles, but drug resistance, disease recurrence and side effects are common. Patients often develop deformities requiring amputations. DNDi are currently running a Phase II/III trial for fosravuconazole to assess if this azole is more effective and safer than the currently used azoles itraconazole and ketoconazole. A comprehensive review of the current antifungal pipeline has recently been published[115].

5. Conclusion

The current treatments used for tropical diseases are sub-optimal or in some cases there are no drugs available. However, recent progress in drug discovery in human African trypanosomiasis, TB and malaria show that with concerted efforts of governments, charities, foundations, product development partnerships, academic institutions and pharmaceutical companies, headway can be made. There is still a long way to go, even in these disease areas. The high attrition rate in clinical trials and issues of resistance means that there is no room for complacency. Further, multiple new agents are required for each disease area to allow combination therapies. Whilst there is progress in some disease areas, in other disease areas, there is much less support and activity.

Figure 1: Deaths and Disability Adjusted Life Years (DALYs) of selected tropical diseases from WHO Cause Specific Mortality (2015)[1] and WHO Disease Burden (2015)[2]. Diarrheal diseases, tuberculosis, HIV/AIDS, malaria and hepatitis are shown separately as they have a much larger impact. Data is shown by WHO region.

Figure 2: Upper panel: The stages of the drug discovery process. Middle panel: generic challenges. Bottom panel: key challenges at particular stages of the drug discovery process.

Figure 3: Key compounds discussed in the text

Box 1: Infants and Children

Many of the infectious tropical diseases disproportionately affect infants and children. In the case of malaria, the majority of deaths occur in children under the age of 5, as they are immune-naïve. Diarrhea is a major problem amongst children, causing hundreds of thousands of deaths per year. The Global Enteric Multicenter Study (GEMS), a case-control study conducted at 7 sites in Africa and South Asia, is the most comprehensive study of childhood diarrhea to date[116,117]. The most common pathogens found on this study were *Shigella spp*, rotavirus, adenovirus 40/41, heat-stable enterotoxin-producing *E. coli, Cryptosporidium spp* and *Campylobacter spp*. In some cases mixed infections were a problem. Some tropical diseases are also associated with malnutrition, growth stunting and impaired cognitive development amongst children, for example cryptosporidiosis, schistosomiasis and soil transmitted helminths[118,119]. In addition, the drug discovery pathway for infants and children is complicated. Pharmacokinetics are much more difficult to predict in infants and children and additional safety testing is required, making clinical trials challenging. Further, ethical regulations in clinical trials for children are more complex.

Box 2: Co-infections

Co-infections are associated with high prevalence and the extensive geographic overlap of some of these diseases. Someone who is already infected with one pathogen in some cases, may have an increased infection risk with another pathogen[118]. Some of the issues around co-infection are:

- Co-infections frequently accelerate disease progression and outcomes as one disease enhances the effect of another. For example, malaria infection increases the viral load of HIV-infected patients, also making it easier for that person to pass on the HIV virus[120]. HIV-TB co-infection is particularly problematic; HIV weakens the immune system allowing latent TB to become activated and progress more rapidly. In turn, TB also accelerates the progression of HIV infection[121].
- Co-infections can result in complications in pregnancy and impair growth and development in children. For example, co-infections of malaria and hookworm can lead to severe depletions in haemoglobin resulting in severe anaemia[122].
- Co-infections can complicate treatments due to drug-drug interactions which can affect efficacy and can give rise to cumulative drug toxicities producing adverse side effects[123]. This is a particular problem in HIV-TB co-infection. Rifampicin, which is commonly used to treat TB, causes induction of cytochrome P450s. The latter metabolise some of the more commonly used anti-HIV drugs[124]. This means careful selection of treatments is required.
- Co-infections can affect how diseases are treated. For example, ivermectin treatment for onchocerciasis may induce severe adverse reactions in some individuals heavily infected with *Loa loa*[125,126].

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Author contributions

All the authors contributed to writing the text.

Author information

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References

1 Global health estimates 2015: Deaths by cause, age, sex, by country and by region, 2000-2015. Geneva, World Health Organization; 2016.

2 Global Health Estimates 2015: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2015. Geneva, World Health Organization; 2016.

3 http://www.who.int/neglected_diseases/diseases/en/.

4 Shepard, D. S., Undurraga, E. A., Halasa, Y. A. & Stanaway, J. D. The global economic burden of dengue: a systematic analysis. *Lancet Infect Dis* **16**, 935-941 (2016).

5 Conteh, L., Engels, T. & Molyneux, D. H. Socioeconomic aspects of neglected tropical diseases. *Lancet* **375**, 239-247 (2010).

6 https://gfinder.policycuresresearch.org/.

7 https://www.ifpma.org/resource-centre/ifpma-facts-and-figures-report/.

8 Wyatt, P. G., Gilbert, I. H., Read, K. D. & Fairlamb, A. H. Target validation: Linking target and chemical properties to desired product profile. *Curr. Topics Med. Chem.* **11**, 1275-1283 (2011).

9 Burrows, J. N. *et al.* New developments in anti-malarial target candidate and product profiles. *Malaria J* **16**, 26 (2017).

A comprehensive discussion of target product and target candidate profiles for malaria.

10 https://www.dndi.org/diseases-projects.

11 Chatelain, E. Chagas disease drug discovery: toward a new era. *J Biomol Screen* **20**, 22-35 (2015).

12 Huston, C. D. *et al.* A proposed target product profile and developmental cascade for new cryptosporidiosis treatments. *PLoS Negl Trop Dis* **9**, e0003987 (2015).

13 Whitehorn, J. *et al.* Dengue therapeutics, chemoprophylaxis, and allied tools: state of the art and future directions. *PLoS Negl Trop Dis* **8**, e3025 (2014).

14 Pawlowic, M. C., Vinayak, S., Sateriale, A., Brooks, C. F. & Striepen, B. Generating and maintaining transgenic *Cryptosporidium parvum* parasites. *Curr Protoc Microbiol* **46**, 20B 22 21-20B 22 32 (2017).

15 Bushell, E. *et al.* Functional Profiling of a Plasmodium Genome Reveals an Abundance of Essential Genes. *Cell* **170**, 260-272.e268 (2017).

16 de Koning-Ward, T. F., Gilson, P. R. & Crabb, B. S. Advances in molecular genetic systems in malaria. *Nat Rev Microbiol* **13**, 373-387 (2015).

17 Lander, N., Chiurillo, M. A. & Docampo, R. Genome editing by CRISPR/Cas9: A game change in the genetic manipulation of protists. *J Eukaryot Microbiol* **63**, 679-690 (2016).

18 Wang, Y. *et al.* A 'suicide' CRISPR-Cas9 system to promote gene deletion and restoration by electroporation in *Cryptococcus neoformans*. *Sci Rep* **6**, 31145 (2016).

19 Zheng, W., Thorne, N. & McKew, J. C. Phenotypic screens as a renewed approach for drug discovery. *Drug Discov Today* **18**, 1067-1073 (2013).

20 Ang, M. L. & Pethe, K. Contribution of high-content imaging technologies to the

development of anti-infective drugs. *Cytometry A* **89**, 755-760 (2016).
21 Horvath, P. *et al.* Screening out irrelevant cell-based models of disease. *Nat Rev Drug Discov* **15**, 751-769 (2016).
22 Fux, C. A., Shirtliff, M., Stoodley, P. & Costerton, J. W. Can laboratory reference strains mirror "real-world" pathogenesis? *Trends Microbiol* **13**, 58-63 (2005).
23 Angulo-Barturen, I. *et al.* A murine model of *falciparum*-malaria by *in vivo* selection of competent strains in non-myelodepleted mice engrafted with human erythrocytes. *PLoS One* **3**, e2252 (2008).

Description of a humanised mouse model for *falciparum* malaria

24 Mikolajczak, S. A. *et al. Plasmodium vivax* liver stage development and hypnozoite persistence in human liver-chimeric mice. *Cell Host Microbe* **17**, 526-535 (2015).
25 Zhan, L. J., Tang, J., Sun, M. M. & Qin, C. Animal models for tuberculosis in translational and precision medicine. *Front. Microbiol.* **8**, 717 (2017).
26 Kramnik, I. & Beamer, G. Mouse models of human TB pathology: roles in the analysis of necrosis and the development of host-directed therapies. *Semin. Immunopathol.* **38**, 221-237 (2016).
27 Myllymaki, H., Niskanen, M., Oksanen, K. E. & Ramet, M. Animal models in tuberculosis research - where is the beef? *Expert Opin. Drug Discov.* **10**, 871-883 (2015).
28 Francisco, A. F. *et al.* Limited ability of posaconazole to cure both acute and chronic *Trypanosoma cruzi* infections revealed by highly sensitive *in vivo* imaging. *Antimicrob. Agents Chemother.* **59**, 4653-4661 (2015).
29 White, N. J. Determinants of relapse periodicity in *Plasmodium vivax* malaria. *Malaria J* **10**, 297 (2011).
30 Barry 3rd, C. E. *et al.* The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. *Nat Rev Microbiol* **7**, 845 (2009).
31 Sanchez-Valdez, F. J., Padilla, A., Wang, W., Orr, D. & Tarleton, R. L. Spontaneous dormancy protects *Trypanosoma cruzi* during extended drug exposure. *eLife* **7**, e34039 (2018).
32 Silver, L. L. A Gestalt approach to Gram-negative entry. *Bioorg. Med. Chem.* **24**, 6379-6389 (2016).

A description of the barriers to compound penetration in Gram-negative bacteria

33 Brown, D. G., May-Dracka, T. L., Gagnon, M. M. & Tommasi, R. Trends and exceptions of physical properties on antibacterial activity for Gram-positive and Gram-negative pathogens. *J. Med. Chem.* **57**, 10144-10161 (2014).
34 Sarathy, J. P. *et al.* Prediction of drug penetration in tuberculosis lesions. *ACS Infect. Dis.* **2**, 552-563 (2016).
35 Fromm, M. F. Importance of P-glycoprotein at blood-tissue barriers. *Trends Pharmacol Sci* **25**, 423-429 (2004).
36 Woodford, N. & Ellington, M. J. The emergence of antibiotic resistance by mutation. *Clin Microbiol Infect* **13**, 5-18 (2007).
37 Irwin, K. K., Renzette, N., Kowalik, T. F. & Jensen, J. D. Antiviral drug resistance as an adaptive process. *Virus Evol* **2**, vew014 (2016).
38 Blasco, B., Leroy, D. & Fidock, D. A. Antimalarial drug resistance: linking *Plasmodium falciparum* parasite biology to the clinic. *Nat. Med.* **23**, 917-928 (2017).
39 Hammer, S. M., Saag, M. S., Schechter, M. & et al. Treatment for adult HIV infection: 2006

recommendations of the international AIDS society–USA panel. *JAMA* **296**, 827-843 (2006).
40 http://www.who.int/malaria/publications/world-malaria-report-2017/report/en/.
41 Wells, T. N., Hooft van Huijsduijnen, R. & Van Voorhis, W. C. Malaria medicines: a glass half full? *Nat Rev Drug Discov* **14**, 424-442 (2015).
42 White, N. J. *et al.* Antimalarial Activity of KAF156 in *falciparum* and *vivax* Malaria. *N. Engl. J. Med.* **375**, 1152-1160 (2016).
43 Macintyre, F. *et al.* A randomised, double-blind clinical phase II trial of the efficacy, safety, tolerability and pharmacokinetics of a single dose combination treatment with artefenomel and piperaquine in adults and children with uncomplicated *Plasmodium falciparum* malaria. *BMC Med.* **15**, 181 (2017).
44 White, N. J. *et al.* Spiroindolone KAE609 for *falciparum* and *vivax* malaria. *N. Engl. J. Med.* **371**, 403-410 (2014).
45 Paquet, T. *et al.* Antimalarial efficacy of MMV390048, an inhibitor of *Plasmodium* phosphatidylinositol 4-kinase. *Sci. Transl. Med.* **9**, eaad9735 (2017).
46 Lim, M. Y. *et al.* UDP-galactose and acetyl-CoA transporters as *Plasmodium* multidrug resistance genes. *Nat Microbiol*, 16166 (2016).
47 Jimenez-Diaz, M. B. *et al.* (+)-SJ733, a clinical candidate for malaria that acts through ATP4 to induce rapid host-mediated clearance of Plasmodium. *Proc. Natl. Acad. Sci. U S A* **111**, E5455-5462 (2014).
48 Baragana, B. *et al.* A novel multiple-stage antimalarial agent that inhibits protein synthesis. *Nature* **522**, 315-320 (2015).
49 McCarthy, J. S. *et al.* Safety, tolerability, pharmacokinetics, and activity of the novel long-acting antimalarial DSM265: a two-part first-in-human phase 1a/1b randomised study. *Lancet Infect. Dis.* **17**, 626-635 (2017).

A description of a clinical trial of an antimalarial including a human challenge trial.

50 Cowell, A. N. *et al.* Mapping the malaria parasite druggable genome by using in vitro evolution and chemogenomics. *Science* **359**, 191-199 (2018).
51 Plouffe, D. M. *et al.* High-throughput assay and discovery of small molecules that interrupt malaria transmission. *Cell Host Microbe* **19**, 114-126 (2016).
52 Hovlid, M. L. & Winzeler, E. A. Phenotypic screens in antimalarial drug discovery. *Trends Parasitol* **32**, 697-707 (2016).
53 McCarthy, J. S. *et al.* Linking murine and human *Plasmodium falciparum* challenge models in a translational path for antimalarial drug development. *Antimicrob Agents Chemother* **60**, 3669-3675 (2016).
54 Stanisic, D. I., McCarthy, J. S. & Good, M. F. Controlled human malaria infection: Applications, advances, and challenges. *Infect Immun* **86**, in press (2018).
55 Amadi, B. *et al.* High dose prolonged treatment with nitazoxanide is not effective for cryptosporidiosis in HIV positive Zambian children: a randomised controlled trial. *BMC Infect. Dis.* **9**, 195 (2009).
56 Manjunatha, U. H., Chao, A. T., Leong, F. J. & Diagana, T. T. Cryptosporidiosis Drug Discovery: Opportunities and Challenges. *ACS Infect Dis* **2**, 530-537 (2016).
57 Hulverson, M. A. *et al.* Bumped-kinase inhibitors for cryptosporidiosis therapy. *J Infect Dis* **215**, 1275-1284 (2017).

Description of development of a series of compounds against Cryptosporidiosis

58 Manjunatha, U. H. *et al.* A Cryptosporidium PI(4)K inhibitor is a drug candidate for cryptosporidiosis. *Nature* **546**, 376-380 (2017).
59 Love, M. S. *et al.* A high-throughput phenotypic screen identifies clofazimine as a potential treatment for cryptosporidiosis. *PLoS Negl Trop Dis* **11**, e0005373 (2017).
60 Field, M. C. *et al.* Anti-trypanosomatid drug discovery: an ongoing challenge and a continuing need. *Nat Rev Microbiol* **15**, 217-231 (2017).

A review encompassing drug discovery for the kinetoplastids.

61 Buscher, P., Cecchi, G., Jamonneau, V. & Priotto, G. Human African trypanosomiasis. *Lancet* **390**, 2397-2409 (2017).
62 Priotto, G. *et al.* Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. *Lancet* **374**, 56-64 (2009).
63 Njamnshi, A. K., Gettinby, G. & Kennedy, P. G. E. The challenging problem of disease staging in human African trypanosomiasis (sleeping sickness): a new approach to a circular question. *Trans R Soc Trop Med Hyg* **111**, 199-203 (2017).
64 Steinmann, P., Stone, C. M., Sutherland, C. S., Tanner, M. & Tediosi, F. Contemporary and emerging strategies for eliminating human African trypanosomiasis due to *Trypanosoma brucei gambiense*: review. *Trop Med Int Health* **20**, 707-718 (2015).
65 Torreele, E. *et al.* Fexinidazole--a new oral nitroimidazole drug candidate entering clinical development for the treatment of sleeping sickness. *PLoS Negl Trop Dis* **4**, e923 (2010).
66 Mesu, V. *et al.* Oral fexinidazole for late-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. *Lancet* **391**, 144-154 (2018).

Results from a human african trypanosomiasis clinical trial demonstrating non-inferiority of fexinidazole compared to NECT treatment.

67 Jacobs, R. T. *et al.* SCYX-7158, an orally-active benzoxaborole for the treatment of stage 2 human African trypanosomiasis. *PLoS Negl Trop Dis* **5**, e1151 (2011).
68 Singh, O. P., Hasker, E., Boelaert, M. & Sundar, S. Elimination of visceral leishmaniasis on the Indian subcontinent. *Lancet Infect Dis* **16**, e304-e309 (2016).
69 https://www.dndi.org/diseases-projects/portfolio.
70 Khare, S. *et al.* Proteasome inhibition for treatment of leishmaniasis, Chagas disease and sleeping sickness. *Nature* **537**, 229-233 (2016).
71 Chatelain, E. Chagas disease research and development: Is there light at the end of the tunnel? *Comput Struct Biotechnol J* **15**, 98-103 (2017).
72 Molina, I. *et al.* Randomized trial of posaconazole and benznidazole for chronic Chagas' disease. *N Engl J Med* **370**, 1899-1908 (2014).
73 Ford, N. *et al.* The WHO public health approach to HIV treatment and care: looking back and looking ahead. *Lancet Infect Dis* **18**, e76-e86 (2018).
74 Meanwell, N. A. 2015 Philip S. Portoghese Medicinal Chemistry Lectureship. Curing hepatitis C virus infection with direct-acting antiviral agents: The arc of a medicinal chemistry triumph. *J Med Chem* **59**, 7311-7351 (2016).
75 Basile, K., Kok, J. & Dwyer, D. E. Zika virus: what, where from and where to? *Pathology* **49**, 698-706 (2017).
76 Wahid, B., Ali, A., Rafique, S. & Idrees, M. Global expansion of chikungunya virus: mapping

the 64-year history. *Int J Infect Dis* **58**, 69-76 (2017).
77 Gyawali, N., Bradbury, R. S. & Taylor-Robinson, A. W. The epidemiology of dengue infection: Harnessing past experience and current knowledge to support implementation of future control strategies. *J Vector Borne Dis* **53**, 293-304 (2016).
78 Coltart, C. E., Lindsey, B., Ghinai, I., Johnson, A. M. & Heymann, D. L. The Ebola outbreak, 2013-2016: old lessons for new epidemics. *Philos Trans R Soc Lond B Biol Sci* **372** (2017).
79 de Wit, E., van Doremalen, N., Falzarano, D. & Munster, V. J. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol* **14**, 523-534 (2016).
80 Boldescu, V., Behnam, M. A. M., Vasilakis, N. & Klein, C. D. Broad-spectrum agents for flaviviral infections: dengue, Zika and beyond. *Nat Rev Drug Discov* **16**, 565-586 (2017).
81 Sissoko, D. *et al.* Experimental treatment with favipiravir for ebola virus disease (the JIKI Trial): A historically controlled, single-arm proof-of-concept trial in Guinea. *PLoS Med* **13**, e1001967 (2016).
82 Warren, T. K. *et al.* Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* **531**, 381-385 (2016).
83 Check Hayden, E. Experimental drugs poised for use in Ebola outbreak. *Nature* **557**, 475-476 (2018).
84 Taylor, R. *et al.* BCX4430 - A broad-spectrum antiviral adenosine nucleoside analog under development for the treatment of Ebola virus disease. *J Infect Public Health* **9**, 220-226 (2016).
85 Warren, T. K. *et al.* Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. *Nature* **508**, 402-405 (2014).
86 Debing, Y., Neyts, J. & Delang, L. The future of antivirals: broad-spectrum inhibitors. *Curr Opin Infect Dis* **28**, 596-602 (2015).
87 https://www.tballiance.org/portfolio.
88 Hoagland, D. T., Liu, J., Lee, R. B. & Lee, R. E. New agents for the treatment of drug-resistant *Mycobacterium tuberculosis*. *Adv. Drug Deliv. Rev.* **102**, 55-72 (2016).
89 Lamprecht, D. A. *et al.* Turning the respiratory flexibility of *Mycobacterium tuberculosis* against itself. *Nat. Commun.* **7**, 12393 (2016).
90 Kakkar, A. K. & Dahiya, N. Bedaquiline for the treatment of resistant tuberculosis: promises and pitfalls. *Tuberculosis* **94**, 357-362 (2014).
91 Matsumoto, M. *et al.* OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. *PLoS Med.* **3**, e466 (2006).
92 Olaru, I. D. *et al.* Novel drugs against tuberculosis: a clinician's perspective. *Eur. Respir. J.* **45**, 1119-1131 (2015).
93 https://www.newtbdrugs.org/pipeline/clinical.
94 Lee, M. *et al.* Linezolid for XDR-TB--Final study outcomes. *N. Engl. J. Med.* **373**, 290-291 (2015).
95 Song, T. *et al.* Linezolid Trough Concentrations Correlate with Mitochondrial Toxicity-Related Adverse Events in the Treatment of Chronic Extensively Drug-Resistant Tuberculosis. *EBioMedicine* **2**, 1627-1633 (2015).
96 Li, X. *et al.* Discovery of a potent and specific *M. tuberculosis* leucyl-tRNA synthetase inhibitor: (S)-3-(Aminomethyl)-4-chloro-7-(2-hydroxyethoxy)benzo[c][1,2]oxaborol-1(3H)-ol (GSK656). *J. Med. Chem.* **60**, 8011-8026 (2017).
97 http://www.who.int/tb/publications/global_report/en/.
98 Tiberi, S. *et al.* Tuberculosis: progress and advances in development of new drugs, treatment regimens, and host-directed therapies. *Lancet Infect Dis* **18**, e183-e198 (2018).
99 Tacconelli, E. *et al.* Discovery, research, and development of new antibiotics: the WHO

priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect. Dis.* **18**, 318-327 (2018).
100 WHO. Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organisation (WHO/EMP/IAU/2017.11). (2017).
101 Baker, S. *et al.* Fitness benefits in fluoroquinolone-resistant *Salmonella* Typhi in the absence of antimicrobial pressure. *eLife* **2**, e01229 (2013).
102 Wong, V. K. *et al.* Phylogeographical analysis of the dominant multidrug-resistant H58 clade of *Salmonella* Typhi identifies inter- and intracontinental transmission events. *Nat. Genet.* **47**, 632-639 (2015).
103 Hotez, P. J. *et al.* Helminth infections: the great neglected tropical diseases. *J. Clin. Invest.* **118**, 1311-1321 (2008).
104 Moser, W. *et al.* Efficacy and safety of tribendimidine, tribendimidine plus ivermectin, tribendimidine plus oxantel pamoate, and albendazole plus oxantel pamoate against hookworm and concomitant soil-transmitted helminth infections in Tanzania and Cote d'Ivoire: a randomised, controlled, single-blinded, non-inferiority trial. *Lancet Infect Dis* **17**, 1162-1171 (2017).
105 Sayasone, S. *et al.* Efficacy and safety of tribendimidine versus praziquantel against *Opisthorchis viverrini* in Laos: an open-label, randomised, non-inferiority, phase 2 trial. *Lancet Infect Dis* **18**, 155-161 (2018).
106 Xiao, S. H., Utzinger, J., Tanner, M., Keiser, J. & Xue, J. Advances with the Chinese anthelminthic drug tribendimidine in clinical trials and laboratory investigations. *Acta tropica* **126**, 115-126 (2013).

Comprehensive review of the discovery and development of tribendimidine, the first new anthelminthic in 30 years.

107 Moser, W. *et al.* Efficacy and safety of oxantel pamoate in school-aged children infected with *Trichuris trichiura* on Pemba Island, Tanzania: a parallel, randomised, controlled, dose-ranging study. *Lancet Infect Dis* **16**, 53-60 (2016).
108 Moser, W. *et al.* Efficacy and tolerability of triple drug therapy with albendazole, pyrantel pamoate, and oxantel pamoate compared with albendazole plus oxantel pamoate, pyrantel pamoate plus oxantel pamoate, and mebendazole plus pyrantel pamoate and oxantel pamoate against hookworm infections in school-aged children in Laos: a randomised, single-blind trial. *Lancet Infect Dis* **18**, 729-737 (2018).
109 Awadzi, K., Opoku, N. O., Attah, S. K., Lazdins-Helds, J. & Kuesel, A. C. A randomized, single-ascending-dose, ivermectin-controlled, double-blind study of moxidectin in *Onchocerca volvulus* infection. *PLoS Negl Trop Dis* **8**, e2953 (2014).
110 Keiser, J. *et al.* Praziquantel, mefloquine-praziquantel, and mefloquine-artesunate-praziquantel against *Schistosoma haematobium*: a randomized, exploratory, open-label trial. *PLoS Negl Trop Dis* **8**, e2975 (2014).
111 Klarmann-Schulz, U. *et al.* Comparison of doxycycline, minocycline, doxycycline plus albendazole and albendazole alone in their efficacy against onchocerciasis in a randomized, open-label, pilot trial. *PLoS Negl Trop Dis* **11**, e0005156 (2017).
112 Guidi, A. *et al.* Discovery by organism based high-throughput screening of new multi-stage compounds affecting *Schistosoma mansoni* viability, egg formation and production. *PLoS Negl Trop Dis* **11**, e0005994 (2017).
113 Mansour, N. R. *et al.* High throughput screening identifies novel lead compounds with

activity against larval, juvenile and adult *Schistosoma mansoni*. *PLoS Negl Trop Dis* **10**, e0004659 (2016).
114 Rajasingham, R. *et al.* Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis* **17**, 873-881 (2017).
115 Perfect, J. R. The antifungal pipeline: a reality check. *Nat. Rev. Drug Discov.* **16**, 603-616 (2017).
116 Kotloff, K. L. *et al.* Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* **382**, 209-222 (2013).

The results of a clinical study into enteric diseases in LMICs

117 Liu, J. *et al.* Use of quantitative molecular diagnostic methods to identify causes of diarrhoea in children: a reanalysis of the GEMS case-control study. *Lancet* **388**, 1291-1301 (2016).
118 Hotez, P. J., Fenwick, A., Savioli, L. & Molyneux, D. H. Rescuing the bottom billion through control of neglected tropical diseases. *Lancet* **373**, 1570-1575 (2009).
119 Checkley, W. *et al.* A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for cryptosporidium. *Lancet Infect. Dis.* **15**, 85-94 (2015).
120 Kublin, J. G. *et al.* Effect of *Plasmodium falciparum* malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. *Lancet* **365**, 233-240 (2005).
121 Mayer, K. H. & Dukes Hamilton, C. Synergistic pandemics: confronting the global HIV and tuberculosis epidemics. *Clin. Infect. Dis.* **50 Suppl 3**, S67-70 (2010).
122 Brooker, S. *et al.* Epidemiology of *Plasmodium*-helminth co-infection in Africa: populations at risk, potential impact on anemia, and prospects for combining control. *Am J Trop Med Hyg* **77**, 88-98 (2007).
123 Blanc, F. X. *et al.* Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N. Engl. J. Med.* **365**, 1471-1481 (2011).
124 Josephson, F. Drug-drug interactions in the treatment of HIV infection: focus on pharmacokinetic enhancement through CYP3A inhibition. *J Intern Med* **268**, 530-539 (2010).
125 Pion, S. D. *et al.* Co-infection with *Onchocerca volvulus* and *Loa loa* microfilariae in central Cameroon: are these two species interacting? *Parasitology* **132**, 843-854 (2006).
126 Hoerauf, A., Pfarr, K., Mand, S., Debrah, A. Y. & Specht, S. Filariasis in Africa--treatment challenges and prospects. *Clin Microbiol Infect* **17**, 977-985 (2011).

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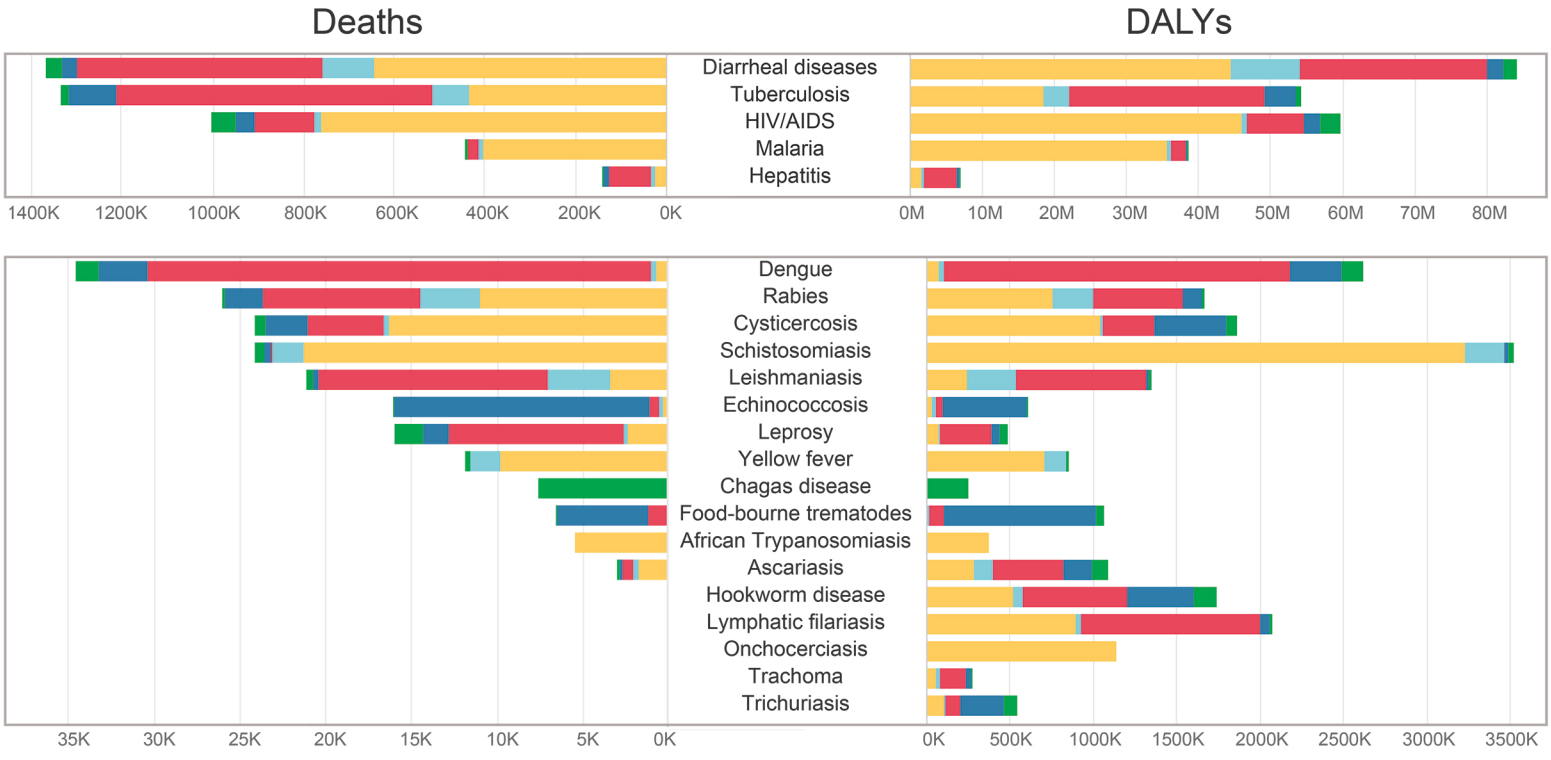
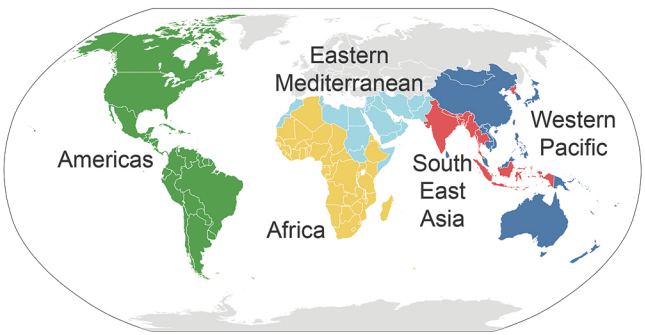


WHO Regions Key



The colours of the subsection on the bar graph relate to the WHO regions on the map

Disease	Pathogen	Type
Diarrheal diseases	Multiple pathogens	Bacteria, Viruses, Protozoan
Tuberculosis	*Mycobacterium tuberculosis*	Mycobacterium
HIV/AIDS	Human immunodeficiency virus	Virus
Malaria	*Plasmodium spp*	Protozoan
Hepatitis	Hepatitis A, B, C, D and E	Virus
Dengue	Dengue virus	Virus
Rabies	Rhabdoviridae	Virus
Cysticercosis	*Taenia solium*	Tapeworm
Schistosomiasis	*Schistosoma spp*	Helminth
Leishmaniasis	*Leishmania spp*	Protozoan
Echinococcosis	*Echinococcus spp*	Tapeworm
Leprosy	*Mycobacterium leprae*	Mycobacterium
Yellow fever	Yellow fever virus	Virus
Chagas diseases	*Trypanosoma cruzi*	Protozoan
Food-bourne trematode	*Clonorchiasis, Opisthorhiasis, Fascioliasis, Paragonimisaisis*	Helminth
African trypanosomiasis	*Trypanosoma brucei*	Protozoan
Ascariasis	*Ascaris lumbricoides*	Soil transmitted helminth
Hookworm diseases	*Ancylostoma duodenale* and *Necator americanus*	Soil transmitted helminth
Lymphatic filariasis	*Wuchereria bancrofti, Brugia malayi, Brugia timori*	Nematode
Onchocerciasis	*Onchocerca volvulus*	Nematode
Trachoma	*Chlamydia trachomatis*	Bacterium
Trichuriasis	*Trichuris trichiura*	Soil transmitted helminth

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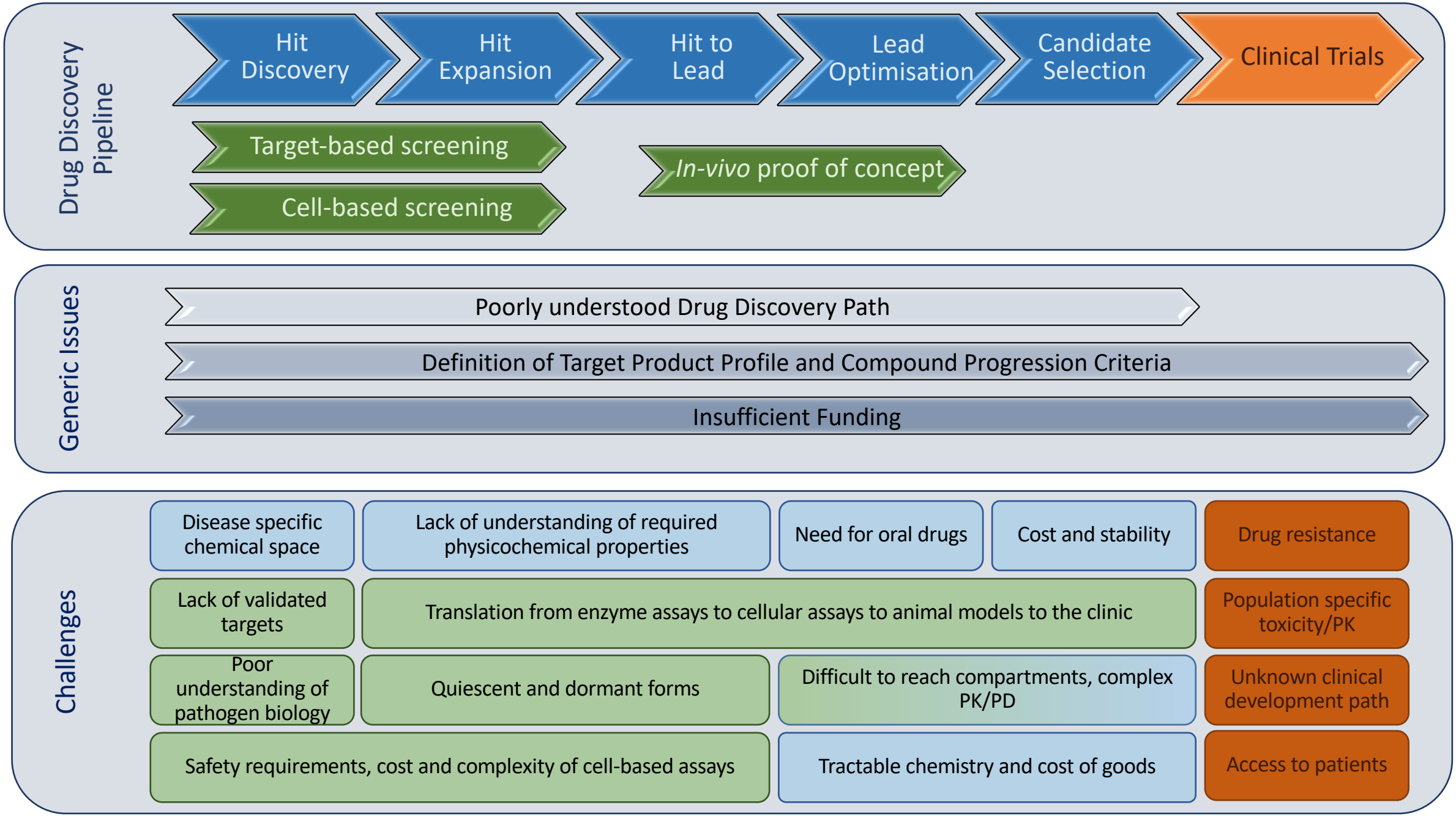
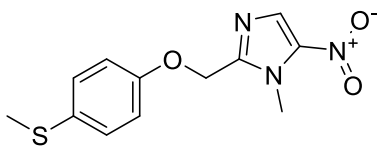
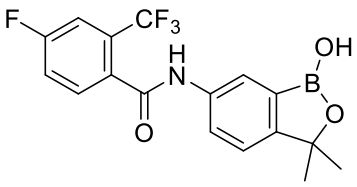

Drug Discovery Pipeline
Hit Discovery
Hit Expansion
Hit to Lead
Lead Optimisation
Candidate Selection
Clinical Trials
Target-based screening
Cell-based screening
In-vivo proof of concept
Generic Issues
Poorly understood Drug Discovery Path
Definition of Target Product Profile and Compound Progression Criteria
Insufficient Funding
Challenges
Disease specific chemical space
Lack of understanding of required physicochemical properties
Need for oral drugs
Cost and stability
Drug resistance
Lack of validated targets
Translation from enzyme assays to cellular assays to animal models to the clinic
Population specific toxicity/PK
Poor understanding of pathogen biology
Quiescent and dormant forms
Difficult to reach compartments, complex PK/PD
Unknown clinical development path
Safety requirements, cost and complexity of cell-based assays
Tractable chemistry and cost of goods
Access to patients

Type of file: figure
Label: 3
Filename: New Figure 3-pmc.pdf

Kinetoplastids Diseases



Fexinidazole



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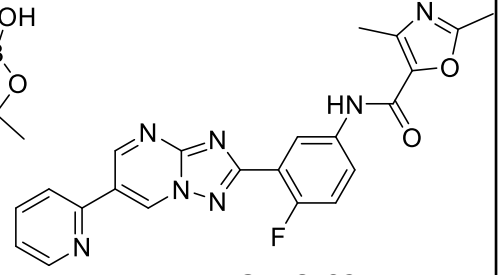
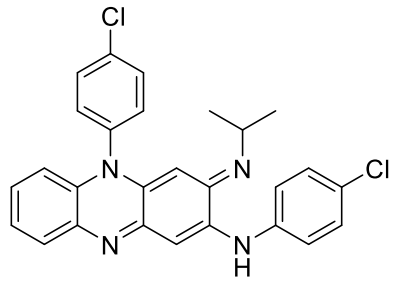
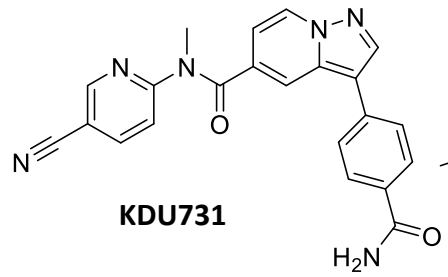


GNF6702

Cryptosporidiosis



Clofazimine



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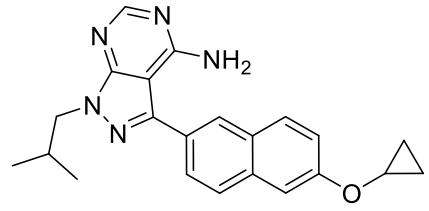

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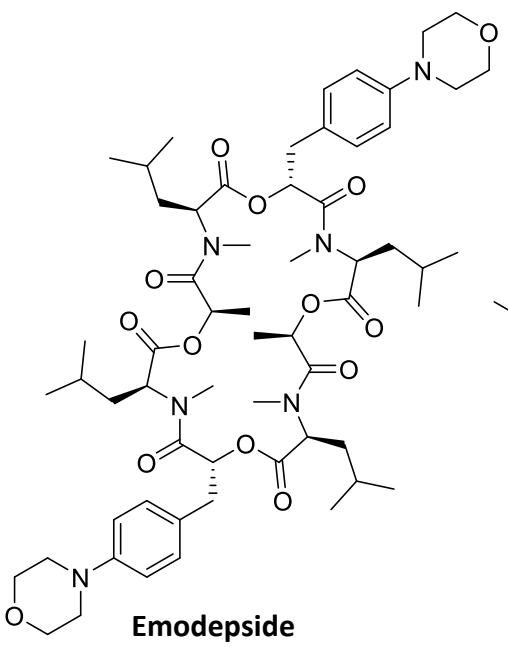
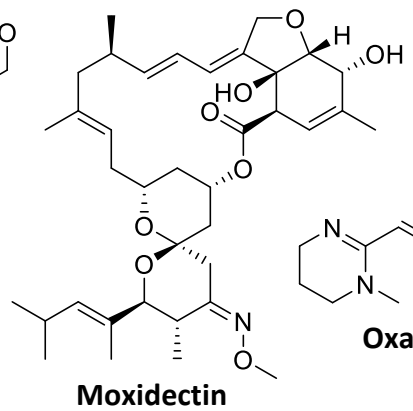
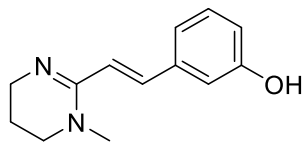
Helminths



Emodepside



Moxidectin



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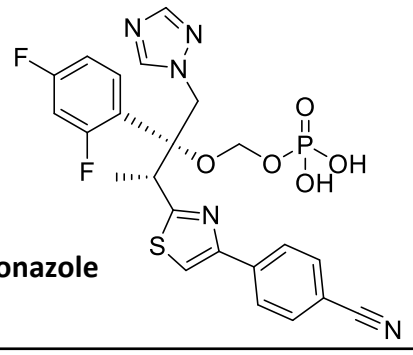
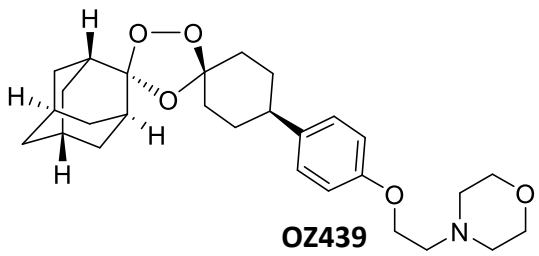


Fosravuconazole

Malaria



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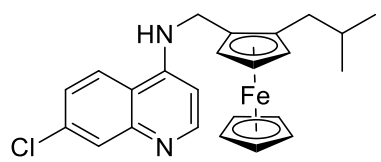

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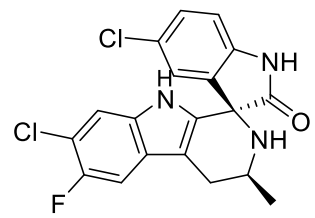

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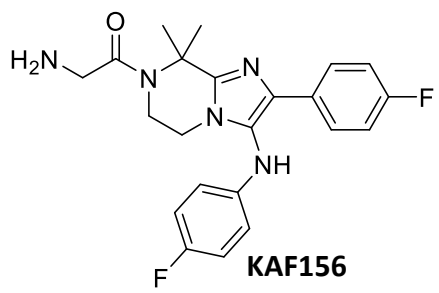

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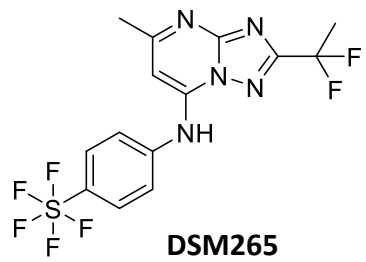

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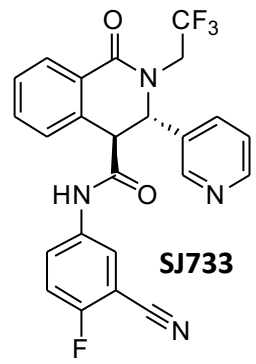

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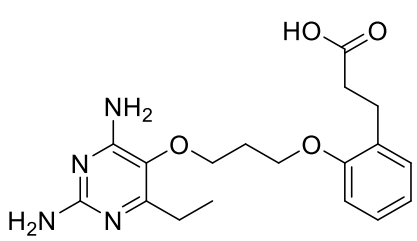

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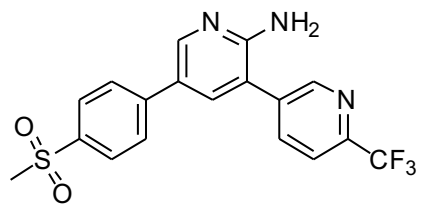

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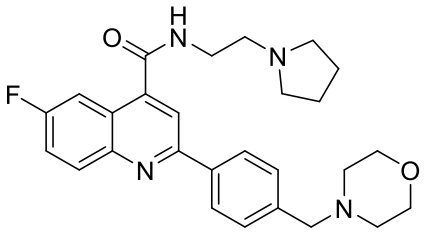

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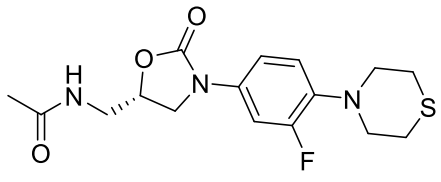

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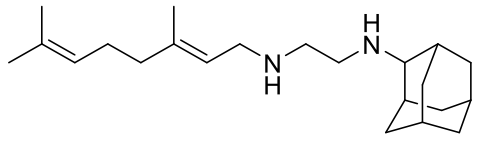

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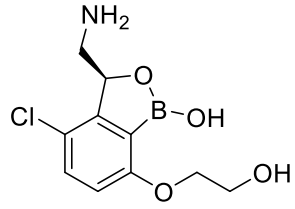

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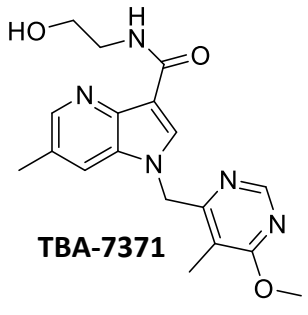

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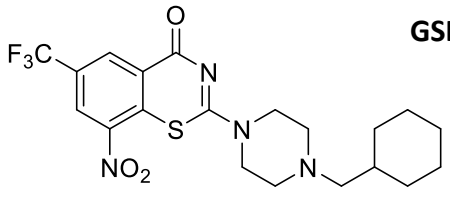

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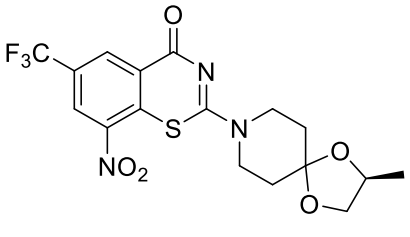

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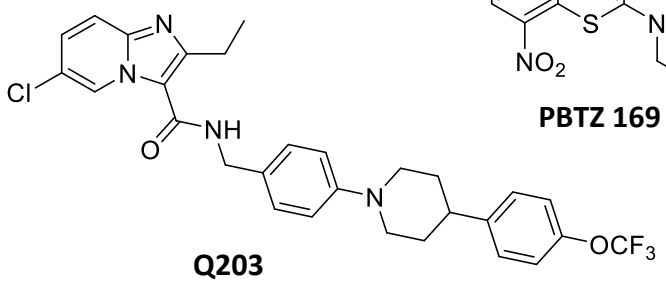

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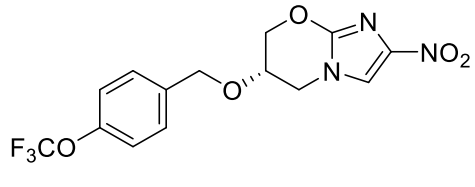
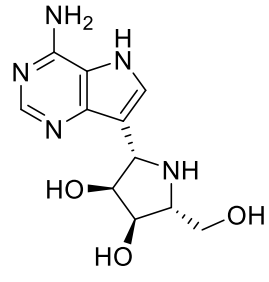


Pretomanid

Viruses



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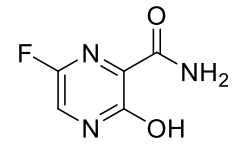
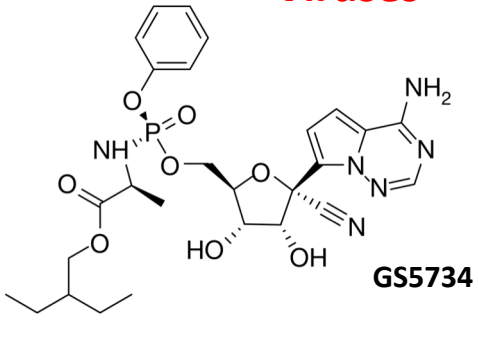


Favipiravir



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